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PATENT COOPERATION TREATY

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SHERIDAN, ROSS

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	30 MAY 2006
Applicant's or agent's file reference 2848-65-PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/02325	24 January 2005 (24.01.2005)	23 January 2004 (23.01.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(8): Please See Continuation Sheet
USPC: 435/4,7.1,7.23

Applicant

THE REGENTS OF THE UNIVERSITY OF COLORADO

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☒ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	16 April 2006 (16.04.2006)	Audrey S. Rham Telephone No. (571) 272-1600

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02325

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☒ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02325

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-17 and 19-25

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02325

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1, 3, 17	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1, 3, 17	NO
Industrial applicability (IA)	Claims 1, 3, 17	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02325

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The claims, as written, are not fully supported by the description and the scope of the claims are broader than justified by the description and drawings.

Claims 4-16, 19 lack support that a gene or combination of genes comprising nucleic acid sequences represented by SEQ ID NO: 1-194 are overexpressed in patients with cancer and its correlation of the genes' overexpression with an EGFR-inhibitor, agonist, or a drug having similar biological activity would likely results in predictable therapeutic benefit.

Claim 2 lacks support in the specification for correlating the identification of a gene having a level of expression in EGFR inhibitor-sensitive cells that is statistically significantly different than the level of expresion of the gene or genes in EGFR inhibitor-resistance cells as potentially being a molecule that interacts with the EGFR pathway to allow or enhance responsiveness to EGFR inhibitors.

Claim 20 lacks support in the specification that a gene from ZEB1 or SIP1 showing differential expression in the presence of gefitinib would result in a benefitical therapeutic effect. Specifically, the nexus is absent and there are no controls to show that the differential expression could not have resulted from toxicity effects.

Claims 21-25 are indefinite because one cannot determined whether "the expression of a gene or genes" refer to the expression of the gene(s) in patient's tumor cells or the expression of the gene(s) that have been correlated with sensitivity or resistance to EGFR inhibitor. Additionally, Claims 21-25 lack support because the specification does not teach comparing the expression level of any gene(s) to noncancerous cell of the same type, to autologous, noncancerous cell from the patient, to gene(s) in a control cell that is resistant to the EGFR inhibitor, to gene(s) in a control cell that is sensitive to the EGFR inhibitor, or to control gene(s) expression levels that have been correlated with sensitivity and/or resistance to the EGFR inhibitor. In short, the specification does not teach any controls for comparison.

Claims 1, 3, 17 will only be examined in part, i.e., with respect to an "EGFR inhibitor," because the specification lacks support that an administration of an EGFR agonist or a drug having substantially similar biological activity as EGFR inhibitor could predictably have a therapeutic benefit.

Claims 1, 3, 17 will also be examined in part, i.e., with respect to the in vitro screening of an EGFR inhibitor because the specification lacks support for comparing the expression of the gene or genes in the patient's tumor cells that is stastistically more similar to the expression levels of the gene or genes and for correlating said expression levels with senstivity or resistance to the EGFR inhibitor.

The phrase "sensistive" is interpreted to mean responsive to an EGFR inhibitor and the term "resistance" is interpreted to mean not responsive to an EGFR inhibitor.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02325

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

Continuation of IPC:
C12Q 1/00(2006.01);**G01N 33/53**(2006.01),**33/569**(2006.01)
A61K 39/00(2006.01),49/00(2006.01)

V. 2. Citations and Explanations:

Claims 1, 3, 17 appear to meet the novelty requirement under PCT Article 33(2) as the prior art references teach a method for selecting a cancer patient who is predicted to benefit from therapeutic administration of an EGFR inhibitor by measuring the protein expression levels, rather than mRNA expression levels of a gene or genes (e.g., Chen et al, US PATENT NO 6,596,878 (Chen et al) 22 July 2003 (22.07.2003) and Uckun et al, US PATENT NO 6,355,678 (Uckun et al) 12 March 2002 (12.03.2002).

Claims 1, 3, 17 lack an inventive step under PCT Article 33(3) as being obvious over US Patent Application Publication 2003/0065156 (Williams et al) 03 April 2003 (04.03.2003).

The claims of the instant invention are drawn to a method to select a cancer patient who is predicted to benefit from therapeutic administration of an EGFR inhibitor comprising providing a sample of tumor cells from a patient to be tested, detecting in the sample the expression of a gene whose expression has been correlated with sensitivity or resistance to an EGFR inhibitor, comparing the level of expression of the gene detected in the patient sample to the level of expression of the gene that has been correlated with sensitivity or resistance to the EGFR inhibitor (Claim 1); wherein the EGFR inhibitor is gefitnib (Claim 3), wherein the expression of the gene is detected by detecting hybridization of at least a portion of the gene or a transcript thereof to a nucleic acid molecule comprising a portion of the gene or transcript thereof in a nucleic acid array (Claim 17).

The US Patent Application Publication teaches a method for identifying novel polynucleotides that are differentially expressed in human cancer cells (paragraphs 004-007, 0203) for screening for antagonists of polynucleotides (page paragraph 113) using nucleic acid arrays (paragraphs 0233-

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

0234). Modification of the method to screen for a cancer patient predicted to benefit from administration of EGFR inhibitors by comparing EGFR mRNA expression levels would be obvious as the prior art clearly establishes the nucleic expression levels can be used to screen for drug candidates (paragraph 0299) and that the expression level of the gene is correlated to prognosis with a disease state (paragraph 0288). It would be further obvious screen for an EGFR inhibitor, such as gefitinib because said EGFR inhibitor is well known in the art.

Claims 1, 3, 17 lack an inventive step under PCT Article 33(3) as being obvious over US Patent Application Publication 2002/0102685 (Sibilia et al) 01 August 2002 (01.08.2002).

The US Patent Application Publication teaches an EGFR inhibitor useful for inhibiting expression of the EGFR gene (paragraph 0041). Modification of a method to select a cancer patient who is predicted to benefit from therapeutic administration of the EGFR inhibitor by testing the level of expression of said gene would be obvious as the prior art clearly establishes that the expression level is associated with prognosis of the disease state.

Claims 1, 3, 17 meet the criteria set out in PCT Article 33(4) and thus meet industrial applicability because the subject matter claimed can be made or used in industry.

CHAPTER I
PCT TELEPHONE MEMORANDUM
FOR
LACK OF UNITY OF INVENTION

PCT No.: PCT/US05/02325

Examiner: Audrey S. Pham

Attorney spoken to: Gary Connell

Date of call: 10 April 2006

☐ Amount of payment approved:

☐ Deposit account number to be charged:

☐ Attorney elected to pay for ALL additional inventions

☐ Attorney elected to pay only for the additional inventions covered by

☐ Group(s):

-- encompassing –

☐ Claim(s):

☒ Attorney elected NOT to pay for any additional inventions, therefore, only the first claimed invention (Group I) covered by Claim(s) 1-17 and 19-25 has been searched.

☒ Attorney was orally advised that there is no right to protest for any group not paid for.

☒ Attorney was orally advised that any protest must be filed no later than 1 month from the mailing of the Search Report (PCT/ISA/210).

Time Limit For Filing A Protest

Applicant is hereby given 1 month from the mailing date of this Search Report in which to file a protest of the holding of lack of unity of invention. In accordance with PCT Rule 40.2, applicant may protest the holding of lack of unity only with respect to the group(s) paid for.

Detailed Reasons For Holding Lack of Unity of Invention:
Please See Continuation Sheet

Note: A copy of this form must be attached to the Search Report.

ATTACHMENT TO CHAPTER I PCT TELEPHONE MEMORANDUM FOR LACK OF UNITY OF INVENTION

Continuation of Detailed Reasons For Holding Lack of Unity of Invention:

1. Claims 1-17, 19-25, drawn to a method to select a cancer patient who is predicted to benefit from therapeutic administration of one component comprising providing a sample of tumor cells from a patient to be tested, detecting in the sample the expression of one gene wherein detection is detected by detecting a nucleic acid whose expression has been correlated with sensitivity or resistance to an EGFR inhibitor, comparing the level of expression of the gene, and selecting the patient as being predicted to benefit from therapeutic administration of the EGFR inhibitor.

NOTE: Claim 4 contains a permutation of amino acid sequences comprising SEQ ID NO: 1-194. These permutations represents a 194! factorial of sequence combinations. As such, Applicant is required to choose ONE combination from 1.33 x 10 exp (361) permuations. Applicant is reminded that any combinations not represented by the elected combination will be withdrawn as being drawn to non-elected inventions.

2. Claims 1-15, 18, drawn to a method to select a cancer patient who is predicted to benefit from therapeutic administration of one component comprising providing a sample of tumor cells from a patient to be tested, detecting in the sample the expression of one gene wherein detection is detected by detecting a protein production whose expression has been correlated with sensitivity or resistance to an EGFR inhibitor, comparing the level of expression of the gene, and selecting the patient as being predicted to benefit from therapeutic administration of the EGFR inhibitor.

NOTE: Claim 4 contains a permutation of amino acid sequences comprising SEQ ID NO: 1-194. These permutations represents a 194! factorial of sequence combinations. As such, Applicant is required to choose ONE combination from 1.33 x 10 exp (361) permuations. Applicant is reminded that any combinations not represented by the elected combination will be withdrawn as being drawn to non-elected inventions.

3. Claim 26, drawn to a method to identify molecules that interact with EGFR pathway to allow or enhance responsiveness to EGFR inhibitors comprising providing a sample of cells that are sensitive or resistant to treatment with gefitinib, detecting the expression of at least oen gene in the gefitnib sensitive cells as compared to the lvel fo expression fo the gene in the gefittinib.

4. Claims 27-39, claims to a plurality of polynucleotides for the detection of the expression of genes that are indicative of sensititivy or resistance to gefitinib.

Species Election

The invention of group 1 contains multiple generic claims that include a plurality of alternatively usable substances or members. These alternative limitations are independent or distinct inventions such that they do not share a common utility or share a substantial structural feature disclosed as being essential to that utility. Because they are not so closely related, a search and examination of the entire claim cannot be made without undue burden. The members of the alternative groupings are described in the following:

Group 1 is generic to a plurality of disclosed patentably distinct species comprising the following therapeutic administrations: EGFR inhibitor, EGFR inhibitor agonist, and a drug having substantially similar biological activity as EGFR inhibitor (Claim 1). These species represent separate and distinct therapeutic administrations with different structures and functions such that one species could not be interchanged with the

other. As such, each species would require different searches and the consideration of different patentability issues.

Additionally, group 1 is generic to a plurality of disclosed patentably distinct species comprising the following genes: comprising ONE sequence selected from SEQ ID NO: 1-194 (Claims 4, 19), ZEB1 (Claim20), SIP1 (Claim 21). These species represent separate and distinct molecules with different structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Additionally, Group 1 is generic to a plurality of disclosed patentably distinct species comprising the following comparison methods: comparing the expression of one gene to the gene in a cell from a non-cancerous cell of the same type (Claim 21), in an autologous noncancerous cell (Claim 21), in a control cell that is resistant to EGFR inhibitor (Claim 23), in a control cell that is sensitive to the EGFR inhibitor (Claim 24). These species represent separate and distinct methods with different objectives, reagents, population samples, and methodologies such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Applicant is required to elect a single disclosed species for examination.

Rule 13.1 of the Patent Cooperation Treaty (PCT) states that an international application should relate to only one invention or to a group of inventions if all inventions are so linked as to form a single inventive concept; i.e., if there is unity of invention. According to Rule 13.2, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The term "special technical features" is referred to as those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art (Rule 13.2). The determination is made on the contents of the claims as interpreted in light of the description and drawing (if any). If there is no special technical feature or if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d).

The inventions listed as groups 1-4 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking groups 1-4 appears to be a method to select a cancer patient who is predicted to benefit from therapeutic administration of an EGFR inhibitor.

However, the technical feature linking groups 1-4 appeared to have been taught by other(s). For example, Chen et al. (US Patent No: 6,596,878, July 2003) teach a method for screening inhibitor compounds of EGFR or HER2 (col 3, lines 39-41) for appropriate administration to an animal or human (col 28, lines 6-10). Specifically, Chen et al. teach EGFR inhibitors have different selectivity in inhibiting the activity of a receptor tyrosine kinase and thus the EGFR inhibitors are selected by measuring growth of cells containing the receptor tyrosine kinase (col 8, lines 56-65). Further, Chen specifically teaches that the EGFR driven disorder are characterized by over-expression of EGFR and that the production of a level of HER2 activity is correlated with a cell proliferative disorder (i.e., as the level of EGFR increases, the severity of the cell proliferative disorder increases) (bridging paragraph col 21-22). The method of the prior art comprises the same method steps as claimed in the instant invention, that is, screening for selecting a patient as being predicted to benefit from therapeutic administration of the EGFR inhibitor. Thus the claimed method is anticipated because the method will inherently lead to correlating the level of expression of genes detected in the patient sample. See Ex Parte Novitski 26 USPQ 1389 (BPAI 1993).

The technical feature linking the inventions of groups 1-4 does NOT constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art. Therefore, restriction for search purpose is proper.

Note: A copy of this form must be attached to the Search Report.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11 "

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.